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A case of drug reaction with eosinophilia and systemic symptoms (DRESS) without a typical precipitant

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A case of drug reaction with eosinophilia and systemic symptoms (DRESS) without a typical precipitant

Clinical record

An 80-year-old man presented with 2 days of fever and a widespread, itchy, non-blanching, erythematous rash involving more than 50% of body surface area over arms, legs, abdomen, back and palms, with sparing of the face and soles of feet (Box 1). He had a history of type 2 diabetes mellitus (treated with sitaglipin 100 mg and metformin 1000 mg modified release daily), hypertension (perindopril arginine 2.5 mg daily), vitamin D deficiency (weekly colecalciferol 125 μg oral) and pernicious anaemia.

He received an adjuvanted trivalent influenza vaccine (TIV) (Fluad; Seqirus, Australia) for the first time 7 days earlier, having tolerated a quadrivalent influenza vaccine in 2017. He had no localising infective or rheumatological symptoms and no medication changes in the preceding year.

On examination, he was febrile (39.9°C), tachycardic and hypotensive. He had the above described rash and inguinal and axillary lymphadenopathy. There was no mucosal involvement or facial oedema. Further physical examination was unremarkable.

The patient received intravenous fluids, flucloxacillin and ceftriaxone, with a presumptive diagnosis of sepsis. Admission investigations revealed a leucocytosis (29.6×10^9 cells/L; normal range [NR], $2.9–12.7 \times 10^9$ cells/L) with neutrophilia (28.0×10^9 cells/L; NR, $1.9–8 \times 10^9$ cells/L) and eosinophilia (0.6×10^9 cells/L; subsequent peak 2.3×10^9 cells/L; NR, $< 5 \times 10^9$ cells/L) (Box 2). There was no lymphocytosis or atypical lymphocytes on blood film. The patient had an acute kidney injury (creatinine 184 μmol/L, baseline 80 μmol/L; NR, 60–110 μmol/L), with bland sediment; liver function was normal. Bacterial cultures of blood and urine were negative. Nasopharyngeal polymerase chain reaction (PCR) was negative for respiratory viruses and *Mycoplasma*. Blood PCR excluded cytomegalovirus, herpes simplex, varicella zoster, and entero- and adenoviruses; human herpes virus-6 was not specifically tested. Serology was negative for syphilis, human immunodeficiency virus, and viral hepatitis, and revealed previous parvovirus infection. Vasculitic screening was negative. The result of a skin biopsy is shown in Box 3.

A diagnosis of drug reaction with eosinophilia and systemic symptoms (DRESS) was made (Registry of Severe Cutaneous Adverse Reaction [RegiSCAR] score 6, classified as

definite[1]). This was likely triggered by influenza vaccination. All usual medications were continued.

Antimicrobials were ceased after 2 days, with negative bacterial cultures, and the patient started taking 50 mg of prednisolone, tapered over several weeks. He experienced a rapid resolution of fever and progressive normalisation of eosinophilia and neutrophilia (Box 2). Renal function returned to baseline by Day 5 and his rash resolved by Day 7, with the emergence of mild skin desquamation during rash resolution. He remains well 4 months later.

Discussion

DRESS is an uncommon, but potentially life-threatening, drug-induced hypersensitivity reaction, with onset usually 2–8 weeks after exposure to the culprit agent. The pathophysiology of DRESS remains unclear, but it involves an aberrant T-lymphocyte response to an antigen, including drugs and infection.

Influenza infection is associated with significant morbidity and mortality, especially in patients at the extremes of age. Since 2018, high dose or adjuvanted influenza vaccination has been recommended in Australia for individuals aged over 65 years. Fluad is an adjuvanted TIV that contains MF59 — an oil-in-water emulsion of squalene (by Novartis) that enhances the cellular and humoral immunogenicity of the vaccine.[2] This results in higher antibody responses than non-adjuvanted vaccines and improved influenza prevention, while maintaining similar safety in older people.[3]

As an immune stimulant, it makes sense that vaccination could trigger DRESS in certain individuals. Indeed, DRESS following non-adjuvanted influenza vaccination has been described and may occur early (< 1 week) after vaccine exposure.[4,5]

In this patient, the strong temporal relationship between vaccination, onset of symptoms and the absence of an alternative trigger suggests a role for adjuvanted TIV as a precipitant of DRESS (Naranjo score 5, classified as probable[6]). While the mechanism is unclear, we hypothesise this could be a direct reaction to a vaccine component, or that non-specific immune activation following vaccination could permit a reaction to a medication, as postulated in previous cases in which each individual was coprescribed a drug typically associated with DRESS (allopurinol[4] and sulfasalazine[5]). None of our patient's medications are commonly associated with DRESS, although case reports exist. Alternatively, the vaccine response could facilitate reactivation of latent herpes viruses, as these have been implicated in the pathogenesis of DRESS and have been included in some diagnostic criteria.[7]

Nevertheless, influenza vaccination is an unusual precipitant of DRESS. Eosinophilic drug reactions following influenza vaccination are rare,[8] and large observational studies of adjuvanted TIV given to older individuals have not reported cases of DRESS.[9,10]

DRESS is an important differential diagnosis in patients presenting with fever and rash. Diagnosis requires a careful history for precipitants, examination for typical features, and investigation to exclude differentials, including infection. While several

medications are classically implicated in the pathophysiology of DRESS, rare reports following vaccination are documented. The management of DRESS includes withdrawal of the causative agent, appropriate supportive care (such as fluids and analgesia), and corticosteroids; patients frequently require hospital admission. Overall, influenza vaccination remains a safe and effective means by which to reduce morbidity and mortality in older individuals.

Lessons from practice

- A drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare, potentially life-threatening condition and an important differential diagnosis in patients with fever, extensive morbilliform or purpuric rash, lymphadenopathy and/or facial oedema. Medication changes in the preceding 2–8 weeks should raise the suspicion for DRESS.
- A diagnosis of DRESS can be made using the RegiSCAR scoring system, which involves examination of the blood and blood film, renal and liver function, skin biopsy, and exclusion of alternative, infective aetiologies. Herpes virus polymerase chain reaction on blood may be a useful adjunct to diagnosis.
- Treatment of DRESS involves cessation of the culprit drug, supportive care, and a weaning course of steroids.
- Enhanced trivalent influenza vaccines are currently recommended for all individuals aged over 65 years in Australia. Vaccination remains a safe and effective means to reduce morbidity and mortality associated with influenza infection.

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[Insert boxes]

[Box 1; mar_mja19.00709_gr1]

1 Images of the rash on presentation to hospital, as seen over the abdomen and arm, showing a violaceous, purpuric, patchy skin eruption with areas of confluence

[Box 2; mar_mja19.00709_gr2]

2 Eosinophils, neutrophils and total white cell count (WCC) since time of presentation and after the initiation of steroids

[Box 3; mar_mja19.00709_gr3]

3 Haematoxylin and eosin staining of skin biopsy sample (magnification × 200 actual) showing a dermal inflammatory cell infiltrate of lymphocytes and scattered eosinophils with minimal dermal oedema, consistent with a drug reaction. There was no specific immunofluorescence staining or features of vasculitis (not shown)